REMARKS

Reconsideration of this application is requested. Claims 21-37 will be active in the application subsequent to entry of this amendment.

The claims have been amended in order to more particularly point out and distinctly claim that which applicants regard as their invention and to more clearly distinguish them from the disclosures of the cited reference. To assist in explaining and demonstrating the changes made to the claims and pointing out basis in the underlying disclosure of the subject application, the previous claims follow with the inserted/deleted material shown in the usual underscore/brackets style plus basis for the term or terminology employed related to the original disclosures shown in parentheses.

1. (Twice Amended) An autoclavable[, non-flocculating aqueous suspension] composition of an aqueous (see claim 1) injectable (see page 1, 1st paragraph) terminally steam sterilized (see page 5, line 20) suspension (see previous claim 1, line 1) in a vial sealed under nitrogen atmosphere (see example 1, 2nd paragraph), said suspension containing particles (page 1, 2nd paragraph and elsewhere) of a water insoluble or poorly soluble biologically active substance [together] with a volume weighted mean particle size of up to 3 μm (see page 3, line 12) with not more than 3000 particles of 10 μm or greater size and not more than 300 particles of 25 μm or greater size, (see page 3, line 14-15) said particles surface stabilized (see page 1, 1st paragraph) with [at least] one or more (see original claim 7) phospholipid surface modifier, and a pharmaceutically acceptable (see claim 5) amount (see claim 4) safe for parenteral administration (see claim 4) of a pharmaceutically acceptable, water soluble polyhdroxy thermoprotecting agent selected from the group consisting of one or a combination of (see page 3, last paragraph) trehalose, lactose, dextrose, sorbitol, dextran, trehalose and mannitol (see page 3 last paragraph and also claim 6), wherein the pH of said suspension is between 5 to 9 (see claim 3), the ratio of said active substance to said surface modifier is 1:1 to 5:1 (see page 8, line 18 to 19), and the amount of said surface modifier is in the range from 0.2% w/w to 5.0% w/w (see former claim 10), wherein said composition is substantially completely devoid of surfactants that require (former claim 2) during terminal steam sterilization (see page 2, line 29) elevation of their cloud point temperature by addition of a cloud point modifier, said composition is substantially devoid of surfactant additives which coagulate on steam sterilization (see page 2, line 31)

[thermoprotecting agent is selected to provide particle size stability during and after terminal steam sterilization], and [wherein a change in] said volume weighted mean particle size is not increased more than [a] two-fold [increase in the volume weighted mean particle size of the particulate aqueous suspension subsequent to] during and after (see page 3, lines 3-4) terminal steam sterilization.

2. (Twice Amended) An autoclavable[, non-flocculating aqueous suspension] composition of an injectable (see page 1, 1st paragraph) non-flocculating aqueous (former claim 1) terminally steam sterilized (see page 5, line 20) suspension (see former claim 1, line 1) under nitrogen in a sealed vial (page 9, lines 10-11), said suspension containing particles (page 1, 2nd paragraph and elsewhere) of a water insoluble or poorly soluble [biologically active] drug (see page 4, line 13) substance with a volume weighted mean particle size of up to 3 μm (see page 3, line 12) with not more than 3000 particles of 10 μm or greater size and not more than 300 particles of 25 μm or greater size (see page 3, line 14-15), [together] said particles surface stabilized (see page 1, 1st paragraph) with [at least] one or more (see original claim 7) phospholipid (see page 4, line 25) surface modifier, and a pharmaceutically acceptable (see former claim 5) amount (see former claim 4) safe for parenteral administration (see former claim 4) of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, wherein the pH of said suspension is between 5 to 9 (see former claim 3), the ratio of [active substance] said drug to said surface modifier is 1:1 to 5:1 (see page 8, line 18 to 19), the amount of said surface modifier is in the range from 0.2% w/w to 5.0% w/w (see former claim 10), and [thermoprotecting agent is selected to provide particle size stability during and after terminal steam sterilization, wherein a change in] said volume weighted mean particle size is not increased more than [a] two-fold during and after terminal steam sterilization [increase subsequent to terminal steam sterilization], and wherein said [the] composition is substantially completely devoid of surfactants that require during terminal steam sterilization (see page 2, line 29) elevation of their cloud point temperature by addition of a cloud point modifier [for further stabilization] and substantially devoid of surfactant additives which coagulate on steam sterilization (see page 2, line 31) [cause destabilization of the formulation].

3. Deleted

4. (Amended) The composition of claim 1 or claim 2, wherein the [composition] suspension also includes an amount of non-surfactant additives such that the [composition] suspension attains an [suitable] osmotic pressure [for] safe for parenteral administration.

5. (Twice Amended) The composition of claim 1 or claim 2, wherein the suspension [composition also includes an amount of non-surfactant additive such that, on] can be diluted[ing the formulation] with water [pharmaceutically acceptable diluent suitable] for parenteral administration [to a pharmaceutically acceptable concentration for parenteral administration, a suitable osmotic pressure for safe parenteral administration of the diluted suspension results].

6. (Amended) The composition of claim [1]2, wherein the [thermoprotecting agent is a pharmaceutically acceptable water soluble] polyhydroxy compound is selected from the group consisting of one or a combination of (see page 3, last paragraph) trehalose, lactose, dextrose, sorbitol, dextran, trehalose and mannitol.

7. (Twice Amended) The composition of claim 1 or claim 2, wherein the phospholipid surface modifier is selected from the group consisting of natural phospholipids and synthetic phospholipids.

8. (No change) The composition of claim 7 wherein the natural phospholipid is an egg phospholipid or soy phospholipid.

9. Deleted.

10. Deleted.

11. (Amended) The composition of claim [1]2 wherein the [composition] suspension also contains pharmaceutical excipients for ophthalmic, peroral, or transdermal administration of the water insoluble or poorly soluble active drug substance.

12. (No change) The composition of claim 1 wherein the active substance is an antifungal agent.

13. (Amended) The composition of claim 12, wherein the [active substance] antifungal agent is itraconazole.

14. (Amended) The composition of claim 1, wherein the active substance is an immuno[-]suppressive agent[drug].

15. (Amended) The composition of claim 14, wherein the [active substance] immunosuppressive agent is a cyclosporin.

16. (Amended) The composition of claim 1, wherein the active substance [drug] is a sterol.

17. (Amended) The composition of claim 16, wherein the [active drug] sterol is [a] alfaxalone.

18. (Amended) A lyophilized or spray dried powder prepared from the composition of claim 1 or claim 2.

19. (Amended) A composition according to claim [1]2, wherein the water-insoluble or poorly water-soluble [active] drug substance is [at a concentration] suitable for either immediate release or sustained release delivery of [the] said drug substance by parenteral administration.

20. (No change) The composition of claim 19 wherein the parenteral administration is intramuscular, or subcutaneous administration.

The examiner will note that elements of former dependent claim 3 that related to pH range, elements of former dependent claim 9 that related to the drug-to-phospholipid surface modifier ratio, and elements of former dependent claim 10 that related to the amount of phospholipid surface modifier have now been incorporated into both claim 21 and claim 22. Note also that elements of former claim 6 that related to the identity of the polyhydroxy compounds have also now been incorporated into claim 21. The pH of the suspension in the composition of this invention is defined as being within a 4-log range i.e., to be between 5 to 9. The ratio of the drug or active substance to surface modifier is in the defined range of 1:1 to 5:1, and the amount of surface modifier is in the range of 0.2% w/w to 5.0% w/w.

The composition consisting of an aqueous suspension of phospholipid-stabilized drug particles, a water-soluble polyhydroxy compound, and a nitrogen atmosphere, all in a sealed vial, is terminally steam sterilized by heating at 121°C for 15 to 30 minutes. The resulting suspension of particles can be administered to a patient by injection. The volume weighted mean particle size (diameter) in the suspension in the presence of the nitrogen atmosphere is 3 micrometers or less. The composition of the current invention also excludes surfactants that require the presence of a cloud point modifier to raise their cloud point temperature during terminal steam

sterilization, and the current composition is also devoid of surfactants that coagulate on steam sterilization.

For convenience a new set of claims is presented. For the reasons explained and pointed out in some detail above, these claims find basis in the original disclosure and thus properly and clearly define applicant's invention. Favorable consideration of these claims and entry of this amendment are solicited.

The sole issue raised in the outstanding Official Action is the pertinence of the disclosure of U.S. patent 5,858,410 to Muller and how the disclosure of that citation, if at all, pertains to the new claims presented above.

The examiner contends that previous claims 1-20 are anticipated by Muller et al. under 35 U.S.C. 102(e) because the disclosure of Muller et al. teaches a drug carrier composition comprising 0.001-30% lecithin plus the compounds glucose, mannose, trehalose, or sorbitol, and 0.1-30% of active. The examiner also contends that Muller et al. teaches parenteral, intramuscular, and subcutaneous administration, and that Muller et al. specifies antimycotic, corticoid, and immuno therapeutics such as cyclosporin.

However, the compositions disclosed in Muller et al. are different from the compositions of the invention as defined by the above claims. The compositions of the current invention are novel over those disclosed by Muller et al. because of the presence of nitrogen that, in a sealed vial, will exhibit varying solubilities in the components of the suspension as a function of temperature and pressure. Muller et al. does not disclose or teach the requirement taught in the current application that nitrogen is needed as a component of the composition. Also, Muller et al. does not teach that the composition of an aqueous suspension containing particles of a water insoluble or poorly soluble biologically active substance or drug that are stabilized with phospholipid together with a nitrogen atmosphere are required to be sealed in a vial. Furthermore, Muller et al. does not teach that particle size stability of the phospholipid-coated particles in the suspension in the composition that includes a nitrogen atmosphere can be maintained during steam sterilization in the presence of certain polyhydroxy thermoprotecting agents that also serve to adjust the osmolality of the suspension to render the suspension in the vial safe for injection. These polyhydroxy thermoprotecting agents in the aqueous particle suspension together with the phospholipid and nitrogen combine in a novel fashion to protect against particle size growth.

Unlike the compositions disclosed in Muller et al. that are compositions of fixed mixtures of ingredients, the compositions of the current invention consist of nitrogen together with a submicron to micron-sized particulate suspension of water-insoluble or poorly water-soluble pharmaceutical agent, the particles stabilized with phospholipid surface modifier, and the aqueous phase containing a pharmaceutically acceptable water soluble polyhydroxy compound. This composition is sealed in a vial and can be autoclaved "without any marked increase in mean particle size" (see Description of the Invention, 1st paragraph). The compositions disclosed by Muller et al., however, are different from those of the current invention in that the Muller et al. compositions produce aggregates and "particle growth" (see Muller et al., column 8, line 21). Muller et al. further teach "The number of particles greater than 5 um rose as a result of exposure of the nanosuspensions to heat and the resulting formation of aggregates" (see Muller et al., column 15, lines 53-55). Muller et al. teach "The standard surfactant concentration in O/W emulsions for parenteral feeding is therefore also 1.2% lecithin (e.g. commercial products such as Intralipid, Lipofundin, Endolipide, Lipovenos etc.)" (see Muller et al., column 7, lines 65 to column 8, line 1). Muller et al. also teach that when the lecithin-containing reference material, Lipofundin, was sterilized "with pressurized steam in an autoclave" ... "the number of particles >5 um per ul" increased substantially (see Muller et al., Example 10, column 15, lines 46-48 and Figure 13, and also the figure on the first page of Muller et al.). Thus, disclosures in Muller et al. with respect to lecithin-containing compositions teach that *particles should grow substantially* when stabilized by lecithin, a phospholipid material. This is contrary to the unexpected findings of the current invention.

The present claims define compositions different from that disclosed in Muller et al. The current invention is a composition of a combination of (1) an aqueous suspension of a particulate water-insoluble or poorly water-soluble biologically active substance or drug in which the particles of the suspension are stabilized by phospholipid, plus (2) a water soluble polyhydroxyl compound dissolved in the suspension, plus (3) nitrogen as a nitrogen atmosphere. This composition of combined ingredients is sealed in a vial. In the suspension component of the current invention, the particles of biologically active substance or drug are surface stabilized by one or more phospholipids. Muller et al. teach that their reference compositions of lecithin-stabilized (i.e., of phospholipid-stabilized) emulsion *particles grow as a result of steam sterilization*. This observation reported by Muller et al. leads one skilled in the art incorrectly to

expect that phospholipid-stabilized particles of the current invention should grow substantially during and after steam sterilization. Fortunately, this is not the case. The particles in the suspension of the current invention are also stabilized against coagulation (i.e., against aggregate formation seen in Muller et al.) and against substantial particle size growth by the presence in addition to the phospholipid of one or a combination of pharmaceutically acceptable water-soluble polyhydroxy compounds. These act as thermoprotecting agents during terminal steam sterilization. These polyhydroxy compounds also act as tonicity modifiers to provide osmolalities in the suspension that permit safe injection of the suspension into human patients.

However, unlike the lecithin-containing reference particles that grow in size during steam sterilization as taught by Muller et al. and unlike the suspensions of Muller et al. that result in the formation of aggregates, the phospholipid-stabilized particles of the composition of the current invention, which composition contains phospholipid stabilizer plus water-soluble polyhydroxy compound plus nitrogen, can be successfully"autoclaved without any marked increase of mean particle size" and without the formation of aggregates. This difference may be explained by the presence of unexpected molecular interactions among the components of the composition of the current invention, and is related to nitrogen's ability to dissolve in the aqueous phase that contains the polyhydroxy compound and also to dissolve in the phospholipid. This nitrogen dissolution disrupts the intermolecular interactions present in the composition such as the intermolecular interactions between the particle surface and the phospholipid, between the phospholipid and the water or polyhydroxy compounds, and between the water and the polyhydroxy compounds. Nitrogen dissolution can alter the ability of the particles to grow as expected by the teachings of Muller et al. Nitrogen-modified molecular interactions present in the current composition because of the nitrogen atmosphere in the sealed vial provide a novel composition that is different from the composition disclosed by Muller et al.

In this regard, it can be postulated that nitrogen molecules from the nitrogen atmosphere that is sealed in the vial together with the aqueous suspension of phospholipid-stabilized particles increasingly dissolve in one or more components of the suspension as a result of increased temperature and pressure gradients experienced during steam sterilization. This change in solubility can modify the equilibrium molecular associations that exist among the components of the composition. If not modified by the presence of nitrogen, these equilibrium molecular associations may otherwise lead, according to the teachings of Muller et al., to increases in

particle size, perhaps by a molecular transport mechanism postulated in the process of Ostwald ripening of particles, which mechanism can function in the absence of the unique combination of components of the current invention. Associations between membrane layers (such as those formed by phospholipids) and gas molecules are well known, for example in the realm of anesthesia. There, gas molecules can dissolve in phospholipid cell membranes and produce modifications to equilibrium intermolecular associations in such membranes and alter or perturb certain electron transfer processes. This gas-dissolved-in-membrane interaction can produce an anesthetic effect that is known to be a function of the amount of (anesthetic) gas administered and thus the amount of gas dissolved in the cell membrane.

Bulk physical chemistry properties such as color, hydrophobicity, and glass transition of individual ingredients and of combinations of ingredients present in a mixture or formulation are often measured and observed in pharmaceutical formulation science. Bulk property concepts such as hydrophobicity derived from these measurements are often extrapolated on a molecular level to explain the average behavior of individual molecules or arrays of molecules, often in terms of bulk molecular interactions in those arrays. However, as the examiner knows, because molecules can be described as arrays of electron density localized by energy constraints around atomic nuclei to form a molecule, it is more appropriate to describe molecular phenomena in terms of relative electron configurations and electron densities.

Intermolecular interactions can influence relative electron configurations of individual molecules in compositions on a molecular level. When a solid particulate surface that can be described as an array of electrons at a given energy level or electron field is stabilized by a membrane-forming substance such as a phospholipid, the membrane exists proximal to the surface of the electron field in part as a result of the average energy associated with electron configurations in the individual phospholipid molecules. This leads to average or equilibrium molecular and atomic spatial configurations (i.e., to "molecular geometries").

Molecular and electron configurations and "molecular geometries" can be influenced, modified, and perturbed by proximal electron distributions in adjacent molecules including other membrane-forming molecules, molecules at the surface of the solid, and molecules in the surrounding environment such as molecules of water and molecules of polyhydroxy compounds dissolved in a suspension. It is a fundamental property of matter that molecular interactions will tend to achieve the lowest possible energy configuration as a function of time.

Factors that can modify relative molecular interactions include applied external fields and gradients such as thermal gradients that can occur in a heating and cooling process leading to kinetic effects and thermodynamic effects that alter relative molecular spatial coordinates; the number molecules in a given volume, i.e., the concentration of various components in a composition; and molecular charge and changes in molecular charge such as, for example, changes in charge induced by addition and removal of protons as a function of pH or chemical reactions such as hydrolytic cleavage of carboxylic acid esters that produces alcohols and carboxylic acids which act as a source of protons. If nitrogen as a gaseous atmosphere is sealed in a vial and is in contact with an aqueous suspension of phospholipid-stabilized particles together with dissolved polyhydroxy compounds of the current invention, water vapor from the aqueous medium will be in equilibrium with the aqueous medium and the nitrogen will dissolve in components of the suspension such as in the aqueous medium containing the polyhydroxy compound and such as in the phospholipid. The solubility of nitrogen as with other solutes can be a function of the temperature.

When the composition of the aqueous suspension of particles and the nitrogen atmosphere that is sealed in a vial is heated during steam sterilization, a positive thermal gradient is applied to the sealed via during heating. The temperature is then stabilized at the sterilization temperature in the sealed vial, and then another (negative) thermal gradient is applied after the vial is removed from sterilization conditions. Because the vial is a closed system, the system will experience changes in pressure as a function of temperature. The temperature and pressure changes will affect the solubility of the nitrogen in the components of the composition such as in the aqueous suspension and in the phospholipid.

The presence of the nitrogen molecules in the aqueous medium and in the phospholipid will alter or perturb various intermolecular interactions that otherwise exist in the absence of the nitrogen. The dissolution of nitrogen molecules in membrane-forming phospholipids and in the aqueous medium containing the dissolved polyhydroxy compounds in the specified pH range can perturb or interfere with molecular associations involved with molecular transport mechanisms and alter kinetic or thermodynamic parameters involved in dissolution of drug or active substance, and/or in transport of the dissolved drug or active substance molecules, and/or in precipitation of such transported molecules similar to that postulated to occur in the process of Ostwald ripening known to produce larger particles. This could explain the lack of substantial

particle size increase in the current invention that is otherwise taught in Muller et al. for phospholipid-containing materials.

Applicant's novel combination of phospholipid, water, polyhydroxy compound, and nitrogen at the specified pH range exhibits an unexpected property of particle size stability contrary to that expected from the disclosure of Muller et al. Muller et al. does not teach that a gas is present or dissolved in the composition. The properties of the compositions of the current invention are different from those disclosed in Muller et al. Thus, the compositions of the current invention are different from the compositions of Muller et al.

For the above reasons it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and allowance are solicited.

Respectfully submitted,

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